HFE gene

hemochromatosis

Normal Function

The *HFE* gene provides instructions for producing a protein that is located on the surface of cells, primarily liver and intestinal cells. The HFE protein is also found on some immune system cells.

The HFE protein interacts with other proteins on the cell surface to detect the amount of iron in the body. The HFE protein regulates the production of another protein called hepcidin, which is considered the "master" iron regulatory hormone. Hepcidin is produced by the liver, and it determines how much iron is absorbed from the diet and released from storage sites in the body. When the proteins involved in iron sensing and absorption are functioning properly, iron absorption is tightly regulated. On average, the body absorbs about 10 percent of the iron obtained from the diet.

The HFE protein also interacts with two proteins called transferrin receptors; however, the role of these interactions in iron regulation is unclear.

Health Conditions Related to Genetic Changes

hereditary hemochromatosis

Researchers have identified more than 20 mutations in the *HFE* gene that cause a form of hereditary hemochromatosis called type 1. Two particular mutations are responsible for most cases of this disorder. Each of these mutations changes one of the protein building blocks (amino acids) in the HFE protein. One mutation replaces the amino acid cysteine with the amino acid tyrosine at position 282 in the protein's chain of amino acids (written as Cys282Tyr or C282Y). The other mutation replaces the amino acid histidine with the amino acid aspartic acid at position 63 (written as His63Asp or H63D).

The Cys282Tyr mutation prevents the altered HFE protein from reaching the cell surface, so it cannot interact with hepcidin and transferrin receptors. As a result, iron regulation is disrupted, and too much iron is absorbed from the diet. This increase in the absorption of dietary iron leads to the iron overload characteristic of type 1 hemochromatosis.

porphyria

Mutations in the *HFE* gene that cause hereditary hemochromatosis also increase the risk of developing the most common form of porphyria, porphyria cutanea tarda.

These mutations are found more frequently in people with porphyria cutanea tarda than in unaffected people.

Researchers suspect that *HFE* gene mutations may trigger this type of porphyria by increasing the absorption of iron. A buildup of excess iron, in combination with other genetic and nongenetic factors, interferes with the production of a molecule called heme. Heme is a component of iron-containing proteins called hemoproteins, including hemoglobin (the protein that carries oxygen in the blood). A blockage in heme production allows other compounds called porphyrins to build up to toxic levels in the liver and other organs. These compounds are formed during the normal process of heme production, but excess iron and other factors allow them to accumulate to toxic levels. The abnormal buildup of porphyrins leads to the characteristic features of porphyria cutanea tarda.

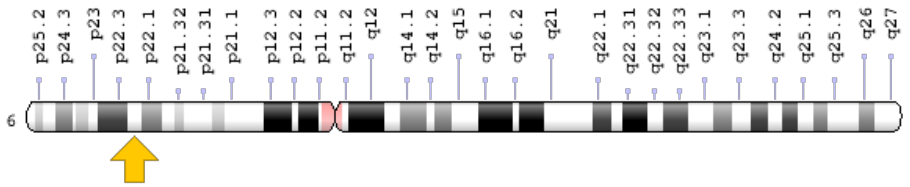
X-linked sideroblastic anemia

The Cys282Tyr mutation, which is a common cause of hereditary hemochromatosis, may also increase the severity of the iron overload in X-linked sideroblastic anemia when it is inherited with a mutation in the *ALAS2* gene. The combination of *HFE* and *ALAS2* mutations leads to more severe signs and symptoms of X-linked sideroblastic anemia by further increasing the absorption of dietary iron, leading to an even greater iron overload.

Chromosomal Location

Cytogenetic Location: 6p22.2, which is the short (p) arm of chromosome 6 at position 22.2

Molecular Location: base pairs 26,087,281 to 26,096,216 on chromosome 6 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- hemochromatosis, genetic; GH
- Hemochromatosis, Hereditary; HH
- Hereditary hemochromatosis protein

- HFE_HUMAN
- HLA-H antigen

Additional Information & Resources

Educational Resources

- NCBI Coffee Break: Variations on a gene: investigating the genetic basis of iron overload
  https://www.ncbi.nlm.nih.gov/books/NBK2311/

GeneReviews

- HFE-Associated Hereditary Hemochromatosis
  https://www.ncbi.nlm.nih.gov/books/NBK1440

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28HFE+gene%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D

OMIM

- HFE GENE
  http://omim.org/entry/613609

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/HFEID44099ch6p22.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=HFE%5Bgene%5D
- HGNC Gene Family: C1-set domain containing
  http://www.genenames.org/cgi-bin/genefamilies/set/591
- HGNC Gene Symbol Report
  http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=4886
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/3077
- UniProt
  http://www.uniprot.org/uniprot/Q30201

Sources for This Summary

- Andrews NC. Molecular control of iron metabolism. Best Pract Res Clin Haematol. 2005 Jun;18(2): 159-69. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15737882
- Camaschella C, Roetto A, De Gobbi M. Genetic haemochromatosis: genes and mutations associated with iron loading. Best Pract Res Clin Haematol. 2002 Jun;15(2):261-76. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/12401307
- Deicher R, Hörl WH. New insights into the regulation of iron homeostasis. Eur J Clin Invest. 2006 May;36(5):301-9. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16634833
- Egger NG, Goeger DE, Payne DA, Miskovsky EP, Weinman SA, Anderson KE. Porphyria cutanea tarda: multiplicity of risk factors including HFE mutations, hepatitis C, and inherited uroporphyrinogen decarboxylase deficiency. Dig Dis Sci. 2002 Feb;47(2):419-26.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/11855561
- Fleming RE, Britton RS, Waheed A, Sly WS, Bacon BR. Pathogenesis of hereditary hemochromatosis. Clin Liver Dis. 2004 Nov;8(4):755-73, vii. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15464654
- Fleming RE, Britton RS. Iron Imports. VI. HFE and regulation of intestinal iron absorption. Am J Physiol Gastrointest Liver Physiol. 2006 Apr;290(4):G590-4. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16537971
- Fleming RE. Advances in understanding the molecular basis for the regulation of dietary iron absorption. Curr Opin Gastroenterol. 2005 Mar;21(2):201-6. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15711214
- Fleming RE. Iron sensing as a partnership: HFE and transferrin receptor 2. Cell Metab. 2009 Mar; 9(3):211-2. doi: 10.1016/j.cmet.2009.02.004.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/19254564
- Ganz T. Iron homeostasis: fitting the puzzle pieces together. Cell Metab. 2008 Apr;7(4):288-90. doi: 10.1016/j.cmet.2008.03.008. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18396134
- Kelleher T, Ryan E, Barrett S, Sweeney M, Byrnes V, O'Keane C, Crowe J. Increased DMT1 but not IREG1 or HFE mRNA following iron depletion therapy in hereditary haemochromatosis. Gut. 2004 Aug;53(8):1174-9.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15247188
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1774138/
- Kowdley KV. Iron, hemochromatosis, and hepatocellular carcinoma. Gastroenterology. 2004 Nov; 127(5 Suppl 1):S79-86. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15508107
- McGregor J, McKie AT, Simpson RJ. Of mice and men: genetic determinants of iron status. Proc Nutr Soc. 2004 Feb;63(1):11-20.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15070436
- Nemeth E, Ganz T. Regulation of iron metabolism by hepcidin. Annu Rev Nutr. 2006;26:323-42. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16848710

- Phillips JD, Bergonia HA, Reilly CA, Franklin MR, Kushner JP. A porphomethene inhibitor of uroporphyrinogen decarboxylase causes porphyria cutanea tarda. Proc Natl Acad Sci U S A. 2007 Mar 20;104(12):5079-84. Epub 2007 Mar 9.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17360334
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1820519/
- Pietrangelo A. Hereditary hemochromatosis--a new look at an old disease. N Engl J Med. 2004 Jun 3;350(23):2383-97. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15175440
- Pietrangelo A. Hereditary hemochromatosis. Annu Rev Nutr. 2006;26:251-70. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16848707
- Sebastiani G, Walker AP. HFE gene in primary and secondary hepatic iron overload. World J Gastroenterol. 2007 Sep 21;13(35):4673-89. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17729389
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4611189/
- Zaahl MG, Merryweather-Clarke AT, Kotze MJ, van der Merwe S, Warnich L, Robson KJ. Analysis of genes implicated in iron regulation in individuals presenting with primary iron overload. Hum Genet. 2004 Oct;115(5):409-17. Epub 2004 Aug 24.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15338274

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